SYNOPSIS OF RESEARCH REPORT 1034932 (PROTOCOL NV20536)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomized, double-blinded, multicenter, dose and duration finding study to evaluate the sustained virologic response of the HCV polymerase inhibitor prodrug (RO5024048) in combination with Pegasys® and Copegus® versus the currently approved combination of Pegasys® and Copegus® in treatment-naive patients with chronic hepatitis C genotype 1 or 4 virus infection. Report No. 1034932. May 2012.		
INVESTIGATORS / CENTERS AND COUNTRIES	Sixty-five investigators were located in 65 study centers in the US (22), Australia (8); Spain (8), Canada (7), France (7), Germany (6), Italy (4), Great Britain (2), and Austria (1).		
PERIOD OF TRIAL	March 30, 2009 to July 15, 2011	CLINICAL PHASE	2
OBJECTIVES	<u>Primary</u> • To study the effects of dose and duration of the HCV polymerase inhibitor prodrug (RO5024048) in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV) versus the currently approved combination of PEG-IFN and RBV (SOC) in treatment-naive patients with chronic hepatitis C (CHC) genotype 1 or 4 virus infection <u>Secondary</u> • To evaluate the safety and tolerability of RO5024048 in combination with PEG-IFN and RBV versus the currently approved SOC • To determine virologic response at defined time points (Weeks 4, 12, 24, 48, and 60) • To evaluate the pharmacokinetics (PK) of RO4995855 when RO5024048 is administered in combination with SOC • To evaluate the resistance profile of RO5024048 in combination with SOC		
STUDY DESIGN	This was a Phase 2, randomized, double-blinded, active controlled, parallel-group study in treatment-naive patients with CHC genotype 1 or 4 virus infection. A total of 424 patients were enrolled into one of five treatment groups to receive triple therapy with RO5024048 + PEG-IFN and RBV (treatment groups A, B, C, and D) or SOC (Group E) (see dose regimens below); treatment was staggered over and within each of two dose cohorts. A total of 100 patients were enrolled into Cohort 1. An initial 25 patients were treated through week 4 before the remaining 75 patients were enrolled. After safety review of data from Cohort 1, patients were randomized into Cohort 2. A sixth group (Group F) was added via Protocol Amendment D to provide open-label triple therapy to those patients in Group E who were deemed treatment failures (Group F results were not included in this report). All patients received study treatment for 24 to 48 weeks, with a treatment-free follow-up period		

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	of 24 weeks.
NUMBER OF SUBJECTS	408 patients
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Males and females between 18 and 65 years of age with treatment naive CHC genotype 1 or 4 and HCV RNA ≥ 50,000 IU/mL, and with chronic liver disease consistent with CHC infection on a biopsy obtained within the past 24 months (36 months for patients with cirrhosis or incomplete/transition to cirrhosis).
TRIAL DRUG / STROKE (BATCH) No.	RO5024048 (500-mg tablets): PT2303C01, PT2303C02, PT2303C03. Placebo: PT2302C01, PT2302C01. RBV (200-mg tablets): 109225, 125154. PEG-IFN: B1004, B1036, B1040, B1006, B1036, B1040.
DOSE / ROUTE / REGIMEN / DURATION	RO5024048, as 500-mg tablets, was administered orally (po) once (qd) or twice daily (bid); PEG-IFN (Pegasys®): 180 ug in 1 mL solution in vials administered subcutaneously (sc) once weekly (qw); RBV (Copegus®): 1000 mg (< 75 kg) or 1200 mg (≥ 75 kg) was administered as 200-mg tablets po qd in split doses (morning/evening). RO5024048 dosing was double-blinded for all patients except those in Group F; SOC dosing was open label. Patients received study treatment as follows: • Treatment Group A: RO5024048 500 mg bid + for 12 weeks followed by SOC for 12 weeks • Treatment Group B: RO5024048 1000 mg bid + SOC for 8 weeks followed by SOC for 16 weeks • Treatment Group C: RO5024048 1000 mg bid + SOC (as for Group A) for 12 weeks followed by SOC for 12 weeks Patients in Groups A, B, and C who achieved a rapid virologic response (RVR, defined as undetectable HCV RNA at week 4) and had viral RNA remain undetectable through week 22 stopped all treatment at week 24. Non-RVR patients received SOC for an additional 24 weeks for total treatment duration of 48 weeks. • Treatment Group D: RO5024048 1000 mg bid + SOC for 12 weeks followed by SOC for 36 weeks; total treatment duration 48 weeks • Treatment Group E: Placebo + SOC for 12 weeks followed by SOC for 36 weeks; total treatment duration 48 weeks • Treatment Group F (SOC treatment-failure patients who were discontinued from Group E and re-assigned to Group F): RO5024048 + SOC open-label
CRITERIA FOR EVALUATION	
EFFICACY:	Primary Parameters: Sustained virologic response (the percentage of patients with undetectable HCV RNA) 24 weeks after end of treatment (SVR-24); SVR for patients in treatment groups A, B, and C with total treatment duration of ≥ 24 weeks or with total treatment

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	duration of ≥ 68 weeks. Secondary Parameters: the percentage of patients with undetectable HCV RNA (< 15 IU/mL) over time; percentage of patients with undetectable HCV RNA) (< 50 IU/mL) over time; the percentage of patients with undetectable HCV RNA (< 15 IU/mL) at last dose; percentage of patients with undetectable HCV RNA at 12 weeks after the last dose of study medication (SVR-12); relapse rate (percentage of patients who achieved a virologic response at end of treatment but had detectable HCV RNA at the last assessment post-treatment).
PHARMACODYNAMICS:	Antiviral activity of RO5024048 in combination with SOC was assessed for all patients at each visit by the quantification of serum HCV RNA viral concentration. Phenotypic and sequence analyses were performed to monitor for the development of drug resistance to RO5024048 in patients who experienced either viral rebound or nonresponse, and in up to 5% of patients that responded while on treatment with RO5024048.
PHARMACOKINETICS:	Pharmacokinetic evaluation was performed for plasma concentrations of RO4995855, RO5012433; and RBV,and included the following parameters: Area under the plasma concentration-time curve from 0 to the end of the dosing period (AUC_{tau}); maximum observed plasma concentration (C_{max}); maximum observed plasma concentration at 12 hours postdose (C_{12h}); time to reach maximum plasma concentration (T_{max}).
SAFETY:	Safety parameters included adverse events (AEs), serious AEs (SAEs), withdrawals from study due to AEs, clinical laboratory values, vital signs, 12-lead electrocardiogram (ECG), and use of concomitant medications.
STATISTICAL METHODS	In summary tables and plots of virologic response, 95% confidence intervals (CI) for individual patient rates were calculated by the Wilson score method without continuity correction,and 95% CI for the difference in response rates between each of the four experimental groups and the SOC group were calculated by using the normal approximation method. Exploratory analyses examined the positive and negative predictive values of early virologic responses on the probability of an SVR. Parameters were summarized using descriptive statistics. All AEs and abnormal laboratory findings were summarized by treatment group; AEs were listed by patient.

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EFFICACY RESULTS:

In the analysis of the primary efficacy endpoint SVR-24 according to actual treatment period, the 4 experimental treatment groups showed no benefit over the SOC group; individual SVR-24 rates for the 500-mg, 1000-mg/8wk, 1000-mg/12wk, 1000-mg nonRVR guided, and SOC groups were 49%, 42%, 33%, 51%, and 51%, respectively. The 1000-mg/12wk RVR-guided and nonRVR-guided groups achieved the highest rates (60% and 57%) of sustained rapid virologic response (HCV RNA undetectable by week 4 and remaining undetectable through week 22, sRVR) among all the treatment groups. The 500-mg and 1000-mg/8wk groups achieved sRVR rates of 38% and 53%, respectively; the SOC group achieved the lowest rate at 18%.

The 5 treatment groups were similar in end-of-treatment virologic response. Relapse of response within the actual 12-week post-treatment period was highest for the 1000-mg/12 wk RVR-guided group. Relapse rates were 31%, 31%, 45%, 29%, and 28% in the 500-mg, 1000-mg/8wk, 1000-mg/12wk, 1000-mg non-RVR guided, and SOC groups, respectively. By 24 weeks post-treatment, an additional 3%, 7%, 7%, 0%, and 3% of relapse was observed in the respective treatment groups.

PHARMACODYNAMIC RESULTS:

All 24 of the GT 4 patients who received triple therapy for 8 or 12 weeks reached undetectable HCV RNA levels by the end of triple therapy. Of the 279 GT 1 patients that completed triple therapy, 11 experienced a partial response with a viral load above 1000 IU/mL at the end of the triple therapy (5 from the 1000-mg/8wk, 5 from the 1000-mg/12wk and 1 from the nonRVR-guided groups). Sequence analysis of the entire NS5B coding region revealed no known RO4995855-resistance mutation (S282T) and no other common amino acid changes that could be involved in the resistance to RO4995855. The lack of phenotypic and sequence changes showed the lack of selection of RO5024048 resistance after 8 or 12 weeks of treatment in combination with PEG-IFN and RBV.

PHARMACOKINETIC RESULTS:

Mean plasma exposures (AUC_{tau} and C_{max}) of RO4995855 were increased with increasing RO5024048 doses from 500 to 1000 mg bid (slightly less than 2-fold) when RO5024048 was given in combination with PEG-IFN/RBV. Ribavirin exposures, as measured by C_{max}, AUC_{tau}, and C_{12h}, were similar in patients receiving RBV with or without MCB.

SAFETY RESULTS:

The 4 RO5024048 + PEG/RBV triple combination regimens had qualitatively similar safety profiles in treatment-naive patients with CHC GT 1 or 4 virus infection; their safety profiles did not differ significantly from patients who received SOC only. No new safety concerns were identified. The most frequent adverse events were headache, fatigue, and nausea. The incidence of adverse events was similar across the 5 treatment groups, with no apparent trends observed. A total of 37 serious adverse events were reported in 32 patients (6% to 11% of patients per treatment group); except for the 1000-mg/12wk group, the incidence of serious adverse events in the experimental groups was less than that of the SOC group (8%). One death occurred during the study (completed suicide by a patient in the 1000-mg/12wk RVR-guided group). The death was considered possibly related to PEG-IFN treatment.

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CONCLUSIONS:

In treatment-naive patients with CHC GT 1 or 4 virus infection, RO5024048 at doses of 500 mg bid and 1000 mg bid in combination with PEG-IFN and RBV for 8 or 12 weeks of treatment did not show benefit over SOC alone, as measured by actual or by scheduled SVR-24. The four experimental treatment groups demonstrated higher rates of complete early virologic response as compared to the control group; however, this pattern was not sustained at treatment Week 24, when response rates in the experimental groups were comparable to the response rate in the SOC group and were a result of virologic rebound after MCB was stopped while receiving PEG-IFN and RBV. Lower SVR was driven by higher relapse rates in the RVR guided arms, particularly among patients who stopped treatment at 24 weeks after achieving a protocol-defined extended RVR (eRVR).

The lack of both phenotypic changes and an absence of NS5B S282T mutation in viral isolates obtained among patients who relapsed or demonstrated viral rebound or breakthrough showed that there was no selection of RO5024048 resistance after 8 or 12 weeks of treatment in combination with SOC.

The 4 experimental treatment groups and the control SOC group demonstrated qualitatively similar safety profiles, suggesting that RO5024048 provided no additional safety burden to the current standard of care with PEG-IFN and RBV in both cirrhotic and non-cirrhotic patients. Further clinical development exploring longer treatment duration is warranted.